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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,178	06/18/2001	Nobuo Nagai	702-010411	5455

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,178	NAGAI ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 8*
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendment filed 24 March 2003 (Paper No. 16) has been entered in full. Claim 7 has been amended and claim 15 has been added. Claims 8-11 have been cancelled. Claims 7 and 12-15 are under examination.

2. The original Information Disclosure Statement filed 31 August 2001 (Paper No. 6) was lost by the USPTO, no fault is laid on the Applicant. The replacement of said IDS has been received and the references therein taken into consideration. No fees concerning replacement of Information Disclosure Statement filed 31 August 2001 (Paper No. 6) are believed due.

3. All references included in the International Search Report have been taken into consideration during the prosecution of the instant application.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

5. The objection to the specification as set forth at pp. 3 ¶5 of the previous Office Action (Paper No. 13, 16 October 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 16, 24 March 2003).

6. The rejection of claim 7 and claims 12-14 under 35 USC §112 2¶ as set forth at pp. 7 ¶13 of the previous Office Action (Paper No. 13, 16 October 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 16, 24 March 2003).

New Objections

7. The specification is objected to because of the following informalities: the specification does not contain a section entitled "**Brief Description of the Drawings**". This objection can be overcome by adding the aforementioned statement at pp. 4 line 35. Appropriate correction is required.

New Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Newly added claim 15 contains the limitation of "administered intracranially" and the Applicant cites "Example 1, subsection 2.5" as support for this limitation. No such limitation or support for it was found in "Example 1, subsection 2.5" for the new limitation. Therefore claim 15 consists of new matter.

Maintained Objections And/Or Rejections

9. Claims **7 and 12-14** are rejected under 35 USC §112 1¶, because the specification, while being enabling for a method for the treatment of focal cerebral ischemic infarction by

administering to an animal or patient an α_2-antiplasmin neutralizing compound in an effective amount that significantly reduces the size of a cerebral ischemic infarct wherein the α_2-antiplasmin neutralizing compound is *plasmin or mini-plasmin,* does not reasonably provide enablement for micro-plasmin, neutralizing compounds with the catalytic domain of plasmin, mutants, and hybrids thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons as set forth in at pp. 3-6 ¶6-12 of the previous Office Action (Paper No. 13, 16 October 2002).

10. The Applicant traverses the 35 USC §112 1¶ paragraph rejection of claims 7 and 12-14 as set forth in at pp. 3-6 ¶6-12 of the previous Office Action (Paper No. 13, 16 October 2002) on the grounds that the administration of α_2-antiplasmin neutralizing agents significantly decrease cerebral ischemic infarct size. In addition, only a "*reasonable number attempts*" are necessary to identify or obtain various α_2-antiplasmin neutralizing compounds useful to practice the invention. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

11. The Examiner maintains, however the rejection under 35 USC 112 ¶1 for claims 7 and 12-14. The specification demonstrates the invention using 50, 100, or 150 μg of human plasmin in a mouse model of cerebral infarction. While it is accepted that the administration of plasmin did result in a decrease in the cerebral infarct size in said mice, the specification is silent on the use of microplasmin, α_2-antiplasmin neutralizing compounds containing the catalytic domain of plasmin, one α_2-antiplasmin neutralizing compounds containing at least on Kringle domain of

plasmin and mutants and hybrids thereof. Thus the skilled artisan is give no guidance on how to make or obtain these other α_2-antiplasmin neutralizing compounds.

12. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to make or use the said compounds. Additionally, a person skilled in the art would recognize that predicting the efficacy of a compound (especially a protein mutant or hybrid) based solely on its performance as a full-length protein is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs in methods of treatment, such a disclosure would not be considered enabling since the state of therapeutic proteins is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

13. The following references are cited herein to illustrate the state of the art of plasmin, plasmin mutants, and hybrids.

14. Concerning the breadth of the claims, the while the specification is silent on the use of mini-plasmin and micro-plasmin, Lapchak et al. (September 2002) "Microplasmin: A Novel Thrombolytic That Improves Behavioral Outcome After Embolic Strokes in Rabbits." Stroke 33(9): 2279-2284 teaches that microplasmin has a salubrious effect on a rabbit small clot embolic stroke model (RSCEM) and rabbit large clot embolic stroke model (RLCEM) (Tables 1-

4). Lapchak et al. (2002) noted, however, that despite the behavioral effect on the rabbit models, microplasmin did not reduce the infarct volume in the models (pp. 2283). Thus, Lapchak et al. (2002) teaches the microplasmin does not satisfy the full scope claims.

15. However, Nagai et al. (15 Mary 2001) "Depletion of circulating α_2-antiplasmin by intravenous plasmin or immunoneutraliz6oin reduce focal cerebral ischemic injury in the absence of arterial recanalization." Blood 97(10): 3086-3092 teaches that both plasmin and mini-plasmin reduce focal cerebral ischemic injury in a mouse model (pp. 3091 and Table 3). On the subject of microplasmin, mutants, and hybrids, Nagai et al. are silent thus leaving a skilled artisan with no guidance as to the nature or effectiveness of these other agents.

16. On the level of predictability in the art, Smalling (15 November 1997) "A fresh look at the molecular pharmacology of plasminogen activators: From theory to test tube to clinical outcomes." Am. J. Health-Syst. Pharm. 54(Suppl. 1): S17-S22 teaches that thrombolytic agents are confronted by two complexities, the administration protocol and the half-life of the molecule. A thrombolytic agent must last long enough to be effective but not too long as to cause undue bleeding in a patient (pp. S18). Also, mutations of the tissue plasminogen activator molecule, ranging from deletions to point mutations varying in their effectiveness and half-life (Figure 1-3). Thus absent specific mutations or modifications of plasmin which may have the desired activity, a skilled artisan cannot predict the usefulness of any given mutant or hybrid absent experimentation.

17. Furthermore on the predictability of the art, Reddy (January 1998) "Newer Thrombolytic drugs for acute myocardial infarction." Indian Journal of Experimental Biology 36(1): 1-15 provides guidance on several mutations and altered plasminogen derivatives (pp. 3-12).

However, Reddy notes the despite the ease with which mutations can be made, their *in vivo* activity, specificity, and half-life are by no means guaranteed leaving a significant burden on the skilled artisan to determine which mutations and derivatives of plasminogen are useful to satisfy the preambles of the claims (pp. 12-13).

18. On the quantity of experimentation needed to practice the invention to its full scope, Bell (1997) "Evaluation of Thrombolytic Agents." Drugs 54(Supplement 3): 11-17 teaches that the undertaking of identifying and evaluating the efficacy of a thrombolytic agent is hampered by the difficulty associated with the undesirable averse effects of the agents especially bleeding (pp. 14). Thus a skilled artisan is confronted with an undue burden of experimentation to insure that the "mutants and hybrids" as claimed fulfill the preamble of claim 7 without unfortunate side effects.

19. Claims **7 and 12-14** are rejected under 35 USC §102(b) as being anticipated by EP 0 631 786 B1 Eibl et al. (17 June 1998) for the reasons as set forth in at pp. 7-8 ¶14 of the previous Office Action (Paper No. 13, 16 October 2002).

20. The Applicant traverses the 35 USC §102(b) rejection of claims 7 and 12-14 as set forth in at pp. 7-8 ¶14 of the previous Office Action (Paper No. 13, 16 October 2002) on the grounds that the Eibl's disclosure does not anticipate the use of compounds such as plasmin, mini-plasmin, micro-plasmin, and monoclonal antibodies to neutralize α_2-antiplasmin. Further Eibl et al. teaches the treatment and prevention of reperfusion injury focusing on events prior to or subsequent to a cerebral ischemic infarction. Also, Eibl et al. teaches the use of lys-plasminogen which is not where the instant claims are directed. Also the claimed invention requires the

specific neutralization of α_2-antiplasmin. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

21. The Examiner maintains, however the rejection under 35 USC 102(b) for claims 7 and 12-14. In regards to the other species, mini-plasmin, micro-plasmin, and monoclonal antibodies to neutralize α_2-antiplasmin, they are not enabled for the instant invention claimed and as such are not subject to an art based rejection. Next, regardless of the claimed activity of the instant claimed proteins, a product inherently possesses the properties of the product. It has been established by the courts that a product inherently possesses characteristics of that product (i.e. including the amino acid sequence of a protein). See, e.g., *Ex parte Gray*, 10 USPQ 2d; *In re Best*, 195 USPQ 430). In addition,

> "the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray*, 10 USPQ 2d 1922 (1989); *In re Best*, 195 USPQ 430 (CCPA 1976).

Moreover, when the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe.*, 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). Lastly it is noted that the courts have held that when the prior art product reasonable appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685).

22. Therefore, even if Eibl et al. did not specifically state the activity of the plasmin administered, it still acting in the manner for which the instant application claims. In Eibl et al. clearly states that plasmin may be used to treat cerebral ischemia which includes infraction (Col. 7 lines 34-50). Thus Eibl et al. meets all the limitations of claims 7 and 12-14 and anticipates the instant application.

Summary

23. No claims are allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher J. Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C Kemmerer

CJN
April 21, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER